Giulliano Peixoto Gonçalves[1], Fabiano Timbó Barbosa[2], Luciano Timbó Barbosa[3], José Lira Duarte[4]

Quality assessment of randomized clinical trial in intensive care

Avaliação da qualidade dos ensaios clínicos aleatórios em terapia intensiva

1. Medical Student at the Universidade Estadual de Ciências da Saúde de Alagoas; Member of the Anesthesiology, Pain and Intensive Care League of Alagoas – Maceió (AL), Brazil.
2. Physician of the Clínica Santa Juliana - Maceió (AL), Brazil; Tutor of the Anesthesiology, Pain and Intensive Care League of Alagoas - Maceió (AL), Brazil.
3. Physician of the Hospital da Agroindústria do Açúcar e do Álcool do Estado de Alagoas - Maceió (AL), Brazil.
4. Physician of the Emergency Unit, Doutor Armando Lages - Maceió (AL), Brazil.

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Author for correspondence:
Fabiano Timbó Barbosa
Rua Comendador Palmeira, 113 – Farol
CEP: 57051-150 – Maceió (AL), Brazil.
E-mail: fabianotimbo@yahoo.com.br

ABSTRACT

Objective: A randomized clinical trial is a prospective study that compares the effect and value of interventions in human beings, of one or more groups vs. a control group. The objective of this study was to evaluate the quality of published randomized clinical trials in Intensive care in Brazil.

Methods: All randomized clinical trials in intensive care found by manual search in Revista Brasileira de Terapia Intensiva from January 2001 to March 2008 were assessed to evaluate their description by the quality scale. Descriptive statistics and a 95 % confidence interval were used for the primary outcome. Our primary outcome was the randomized clinical trial quality.

Results: Our search found 185 original articles, of which 14 were randomized clinical trials. Only one original article (7.1%) showed good quality. There was no statistical significance between the collected data and the data shown in the hypothesis of this search.

Conclusion: It can be concluded that in the sample of assessed articles 7% of the randomized clinical trials in intensive care published in a single intensive care journal in Brazil, present good methodological quality.

Keywords: Health evaluation; Randomized controlled trials as topic; Publications; Intensive care units

INTRODUCTION

The randomized clinical trial is a type of prospective study that compares the effect and value of interventions in human beings, involving one or more groups of intervention and at least one control group, with randomized allocation of participants and using control measures.[1,2] In the majority of cases Intervention under consideration is compared to the most common and more adequate procedure to date. Should there be no such procedure; the experimental group is compared to a placebo group.[1] Randomized clinical trials are viewed as studies that form the basis for the advance of science, because they have less possibility of biases during the investigation of the phenomenon of interest.[3]

Methodological quality assessment enables the reader to analyze a survey's performance and verify the applicability of these findings in his daily clinical practice. Some authors already published their results related to methodological quality assessment in other areas in or outside of medicine, with variable results, as there are few articles with good methodological quality.[4-7]

The objective of this survey was to assess the quality of original articles of the randomized clinical trials in the field of intensive care in Brazil.

METHODS

This survey was submitted to the Committee on Ethics in Research of the Universidade de Ciências da Saúde of Alagoas (protocol 861). A term of informed consent is not applicable in this type of survey. The authors were in charge of the expenses inherent to this survey. The hypothesis tested in this survey was that 5% of the original articles of randomized clinical trials published on intensive care in Brazil were of good methodological quality.

This was a descriptive study for assessment of the quality of randomized clinical trials. Inclusion criterion was: original article of a randomized clinical trial published on intensive care in Brazil. Exclusion criteria were: articles regarding research with animals, articles with incomplete descriptions and original articles involving the pediatric age bracket.

The primary variable analyzed was quality of randomized clinical trials, defined as the probability that a clinical trial will generate unbiased outcomes.[8] Secondary variables were: forwarding of the survey to a Committee of Ethics in Research, use of the informed consent, description of the funding source, sample size calculation, site of origin, statistical test utilized and classification of the type of study.

Original articles from the "Revista Brasileira de Terapia Intensiva" published from January 2001 to March 2008, were analyzed by a manual search for the words random, randomized, double blind, placebo or any other words suggesting that the article was about a randomized clinical trial. Titles, summaries and key words were initially reviewed to separate randomized clinical trials.

Randomized clinical trials were separated, read in their entirety and submitted to quality assessment using the quality scale that can be seen in chart 1.

The quality scale assessment criteria used in the survey were:[8] randomizing, double blind masking and the set of losses and exclusions. These items may be described as follows:

a) For randomization: the method of generating the randomized sequence was considered appropriated when it permitted that each participant had the same chance of receiving each intervention and when the researcher was unable to foresee which would be the next treatment.

b) For double blind masking: a study was considered double blind when the term double blind was used. The method was considered appropriate when neither the patient nor the person in charge of data collection were able to identify the type of treatment given to each one, or in absence of this statement, if the use of an identical placebo or imitations were mentioned.

c) For the losses and exclusions: participants who entered the study but did not fulfill the observation period or were not included in the analysis and who were described by the authors of original articles. Number and reasons for losses in each group must be stated. When there are no losses, this must also be stated in the article. When there was no description of loss, the item was ascribed a zero.

A maximum of five points could be achieved by this scale: one point for each yes, an additional point for an adequate randomization method and another additional point for an adequate masking method.

When the term double blind was not mentioned,

Chart 1 –Items of the quality scale

	*Quality scale
1.a	The study was described as randomized (use of words as "random", "randomized" "randomization")?
1.b	Was the method adequate?
2.a	Was the study described as double blind?
2.b	Was the method adequate?
3.	Was there a description of losses and exclusions?

Source Translated: Greenfield ML, Rosenberg AL, O'Reilly M, Shanks AM, Sliwinski MJ, Nauss MD. The quality of randomized controlled trials in major anesthesiology journals. Anesth Analg. 2005;100(6):1759-64.[4]

*Scoring: each item (1, 2 and 3) receives one point for a yes answer or zero for a no answer. One additional point is attributed if, in the item1, the method of generation of the randomized sequence was described and adequate and, in item 2 if the double blind masking method was described and adequate. One point is deducted in question 1, the method for generation of a randomized sequence was described, but inadequately and, in question 2, if it was described as double blind, but inadequately.

however there was a description of the patient's and researcher's masking of the variables, this item was scored in the quality scale. A study was considered to be of poor quality when it had only two points or less on the quality scale.[8]

Original articles of randomized clinical trials were analyzed and classified for concealment of allocation as follows:

A – Concealment of allocation properly performed and described;[2]

B – Study was described as randomized, but there is no description of randomization nor of concealment of allocation;

C – The study was described as randomized, but the survey method was inadequate, such as: use of the number on medical charts; birth date; alternation of the week days or any other form that had not been considered transparent for the authors of this survey;

D – The study was not a randomized clinical trial.

Articles that were not about a randomized clinical trial were analyzed to confirm their exclusion from the quality assessment and in the search for secondary variables. Secondary variables were also analyzed in the original articles of randomized clinical trials.

Descriptive statistics were used in addition to calculation of the 95% confidence intervals (CI 95%) for results of the methodological quality analysis. Survey data were compared with those of the hypothesis using the Chi-square, considering a 5% significance level.

RESULTS

One hundred and eighty five original articles on intensive care, published in Brazil were found and analyzed. Of these 185, 15 were initially classified as randomized clinical trials.[9-23] These 15 original articles were analyzed regarding concealment of allocation, and six articles[17,19-23] (40%) ranked as A, other six articles[10,13-16,18] (40%) ranked as B, two articles[11,12] (13.3%) as C and one article[9] (6.7%) that was not a randomized clinical trial was ranked as D.

Quality analysis could only be performed in 14 original articles of randomized clinical trials because one article[9] was excluded from this analysis. Results of the quality assessment disclosed that 7% (1/13) of the articles were of good quality[22] (Table 1). Score distribution on the quality scale was: zero for 8 (57.2%) original articles[10-16,18] 2 points for 5 (35.7%)[17,19-21,23] and 4 points for one (7.1%) original article that presented good methodological quality.[22]

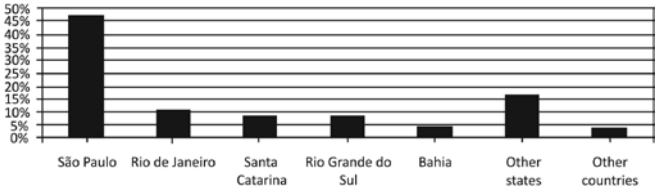
Table 1 – Quality of the original articles of randomized clinical trials in intensive care in Brazil

Quality	N	%	CI 95% (%)
Good	01	7.1	0 to 20.5
Bad	13	92.9	79.5 to 100

CI – Confidence interval; N – number of original articles

The assessment of the secondary variables of all original articles showed that: 110 (59.5%) original articles described submitting the project to a Committee of Ethics in Research, 53 (28.6%) described use of informed consent, 19 (10.3%) described sample size calculation, 146 (78.9%) described the variables analyzed, 118 (63.8%) described inclusion criteria, 90 (48.6%) described exclusion criteria and in only 3 (1.6%) was there a description of the funding source.

Regarding origin of the original articles, it was noted that the largest contribution came from the state of São Paulo with 88 (47.3%) original articles (Graph 1).



Graph 1 – Origin of the original articles on intensive care published in Brazil

Classification of the original articles by type of study is presented in table 2, and the cohort study was the most common, described in 106 (57.3%) of original articles.

Table 2 – Classification of the studies of original articles published on intensive care

Type of study	N	%
Coohort	106	57.3
Cross-sectional	42	22.7
Randomized clinical trial	15	8.1
Case-control	8	4.3
Meta-analysis/Systematic Review	8	4.3
Others	6	3.2

N – number of original articles.

Results of the statistical tests used in the original articles are shown in table 3. The test most often used was the Chi-square in 72 (38.9%) articles, followed by the Student's t test in 59 (31.9%) articles.

Table 3 – Statistical tests used in the original articles on intensive care in Brazil

Statistical test	N	%
Chi-square	72	38.9
Student's t	59	31.9
Fisher	40	21.6
Mann Whitney's U	36	19.5
Variance analysis	25	13.5
Wilcoxon	18	9.7
Logistic regression	18	9.7
Multivariate analysis	13	7.0
Kruskal-Wallis	7	3.8
Others	51	27.6
Did not use (did not describe alpha or p)	35	18.9

N – number of original articles.

Results of the quality analysis of the original articles on randomized clinical trials of this survey were compared with data of the hypothesis and there was no statistical significance (p=0.71).

DISCUSSION

Currently, randomized clinical trials are being described as the gold standard for the assessment of therapeutic issues in health.[24] This type of study reduced the probability of obtaining biased data in a survey.[25] Occurrence of systematic error may be avoided by using randomization masking principles and analysis of all the recruited subjects.[26]

In this survey 14 original articles of randomized clinical trials were found, however only one presented good methodological quality according to the quality scale.[8] The fact that the authors state that the study was randomized does not warrant to the reader or those assessing the article, that it truly was a clinical trial. The randomization principle in this type of study means that the allocation of the surveyed subjects to these study groups must be randomized,[1] participants must have the same probability of receiving interventions as well as being tested regarding their control.[27] If this principle is respected and adequately preformed, randomization reduces risk of systematic errors balancing the risk factors that could influence the clinical outcome to be measured.[28] Some of the authors analyzed did not describe the randomization method and therefore lost the point for this item on the scale.

When assessing masking it was perceived that most authors, directly or indirectly mentioned that there was masking, but did not describe it adequately. The masking principle states that, whenever possible it must be guaranteed that individuals involved as subjects of survey as well as those obtaining the data, do not know which group is receiving intervention or belongs to the control, thus being characterized as double-blind.[29] Masking helps to avoid occurrence of biases due to subjectivity of the researcher as well as of the patients.

A joint description of losses and exclusions that took place after randomization of patients was not found in any of the 14 original articles, therefore no article scored in this item. It is important that the reader has access to the rates and reasons of these losses and exclusions to enable him to assess the feasibility of performing the intervention in his daily practice.

In this survey it was observed that 100 (59.5%) original articles mentioned contact with the Research Ethics Committee, 53 (28.6%) mentioned use of the informed consent and, 3 (1.6%) articles described a funding source. These items were also analyzed by other scales and lists as integral part of the methodological quality assessment and the description gives quality and credibility to the publication.[30,31] Such items should be described in all publications regarding research with human beings.

In this survey it was observed that 19 (10.3%) original articles described sample size calculation. Sample size has an inverse influence on the p value, that is why, very large samples tend to present low p values and lead to errors in decision making concerning the differences found in the survey.[32] Failure to present sample size calculation jeopardizes the validity of outcomes in any survey.

In this survey 146 (78.9%) original articles described the analyzed variables, 118 (63.8%) described inclusion criteria and 90 (48.6%) the exclusion criteria. Description of these items leads to a better understanding of eligibility criteria used. This permits the reader of original articles to judge if it is possible to extrapolate results found in a survey to patients attended in daily practice.[33]

The state of São Paulo had the largest contribution of original articles 88 (47.3%) published. These results can be explained by the larger number of universities, researchers, training centers and scientific events in that city.

Classification of the original articles disclosed that the most frequent survey was the cohort study with 106 (57.3%) articles. This portrays the authors' intention to carry out a survey involving an intervention, however the best way to confirm the effect of a treatment is the randomized clinical trial.[2]

The statistical test most often used is the Chi-square (38.9%). Tests of the hypothesis are expressed in p values that represent the probability of an event taking place in a sample, even if this event is null in the populations that originated the sample.[32] The Chi-square serves to analyze the proportions of the categorical variables and together with the Student's t test may be considered as one of the most often used in health surveys.[33]

Comparison between data of this survey and the formulated hypothesis disclosed that there was no statistical significance (p=0.7). When results are negative and there is no mention of sample size calculation, some authors state that the publication regarding the survey does not deserve any credit by the readers.[33] For this reason we calculated sample size after concluding the survey considering a hypothesis of 5%, an absolute precision of 4% and a significance level of 5% and obtained as an outcome 114 original articles. This number of original articles needed to confirm our hypothesis was lower than the number of articles assessed in this survey, confirming our results that the number of good quality original articles is as low as 5%.

Limitations of this survey were: use of only one scale for quality assessment, assessment of only one of the Brazilian journal that publishes intensive care in Brazil and quality assessment by only one reviewer of the articles. The quality scale used in this survey[8] assesses only the items of internal validity, neglecting those of external validity and the statistical method utilized. Other forms of the methodological quality assessment could also have been used such as individual items and lists.[31] Assessment of only one journal prevented the authors from observing the clinical trials carried out in Brazil but published in other journals, besides Brazilian works published in international journals. It is recommended that more than one reviewer assesses the articles and that discrepancies be resolved by consensus meetings, as such conduct would help to reduce biases.[8]

CONCLUSION

It can be concluded that in the sample of articles assessed, 7% of the randomized clinical trials on intensive care published in one of the Brazilian journals, are of good methodological quality.

RESUMO

Objetivo: O ensaio clínico aleatório é um estudo prospectivo que compara o efeito e o valor das intervenções em seres humanos, utilizando um ou mais grupos contra o grupo controle. O objetivo deste estudo foi avaliar a qualidade dos ensaios clínicos aleatórios publicados em terapia intensiva no Brasil.

Métodos: Todos os ensaios clínicos aleatórios encontrados através da busca manual na Revista Brasileira de Terapia Intensiva de janeiro de 2001 a março de 2008 foram analisados para avaliar sua descrição através da escala de qualidade. Foi utilizada uma estatística descritiva e intervalo de confiança de 95% para a variável primária. A variável primária foi a qualidade dos ensaios clínicos aleatórios.

Resultados: Foram encontrados 185 artigos originais, sendo 14 de ensaios clínicos aleatórios. Apenas um artigo original analisado (7,1%) mostrou-se de boa qualidade. Não houve significância estatística entre os dados coletados e os dados mostrados na hipótese desta pesquisa.

Conclusão: Pode-se concluir que na amostra de artigos avaliada 7% dos ensaios clínicos aleatórios em terapia intensiva publicados em uma revista no Brasil são de boa qualidade metodológica.

Descritores: Avaliação em saúde; Ensaios clínicos controlados aleatórios como assunto; Publicações; Unidade de terapia intensiva

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